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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,304	08/06/2001	Ruth Katz	UTSC:658US/SLH	1430

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	7

DATE MAILED: 07/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,304	KATZ ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *30-56, 67, 83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29,57-66,68-82 and 84-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 1-29, 57-66, 68-82, 84-88 in Paper No. 6 is acknowledged. Prior to allowance of the claims, applicant is required to cancel non-elected subject matter from the claims.

Priority

2. This application claims priority to provisional application 60/222,811, filed August 4, 2000.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 4-29, 57-66, 68-82, 84-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting loss of herterozygosity using a RPL 14 probe as indicative of non-small cell lung cancer, does not reasonably provide enablement for detecting any aberration using a RPL 14 probe as indicative of any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of identifying subjects at risk for the development of any cancer using an RPL14 gene probe to detect any aberration as compared to the wild-type.

The specification teaches a table which "provides an organized view of 12 patients suffering from lung cancer" (page 40, lines 8-10). It appears that the "a" sample from each patient is the non-tumorous bronchous, whereas the "b" sample from each patient is the tumorous sample. As seen in Table 1, each "a" sample had a smaller percentage of deletions (page 40, Table 1). The specification teaches "initial data shows a promising correlation between the deletion percentage and survival of a patient." The specification fails to particularly articulate what the correlation between the deletion and the survival of a patient. Moreover, it is unclear whether the increase in percentage of deletion of RPL14 gene is significantly associated with tumorous tissue or whether the showing is merely "initial data" which requires further studies and analysis. Additionally, the specification teaches that an analysis of numerous dissociated tumors with their adjacent bronchi indicated that DNA probes from 3p and 10q are associated

with smoking and appear to predict for the development of non-small cell lung cancer as well as overall survival (page 42, lines 24-28). The specification also teaches that "non-smokers who develop lung cancer have much higher rates of deletions, higher even than smokers and that these results are significant ($p<0.001$)" (page 43, lines 1-2).

The art namely, Shriver et al. (Mutation Research Genomics, Vol. 406, No. 1, pages 9-23, November 1998) teaches chromosome 3p is consistently deleted in lung cancer, oral squamous cell carcinoma and renal cell carcinoma (abstract). Shriver teaches isolating a gene located at 3p21.3, namely the ribosomal protein L14 gene (RPL14)(abstract). Shriver teaches that "genotype analysis of RPL14 shows that this locus is 68% heterozygous in the normal population, compared with 25% in non-small cell lung cancer (NSCLC) cell lines ($p = 0.008$)" (abstract). Shriver teaches using FISH to identify the location of the RPL14 gene (page 12, col 2). Shriver teaches that DNA from cells and cell lines derived from six matched normal and tumor samples were analyzed (page 16, col 1). Three tumors showed loss of one RPL14 allele while the remaining three showed alterations in the length of the trinucleotide repeat (Table 3, page 16, col 1). Shriver teaches that heterozygosity of RPL14 was analyzed in squamous cell carcinoma of the head and neck (SCCHN) and the tumors exhibited normal levels of herterozygosity (page 16, col 2). Shriver teaches that the aberration of trinucleotide repeat differences was not statistically significant between lung cancer cases and race-matched controls (page 18, col 1). Shriver teaches that RPL14 is an important event in lung carcinogenesis in addition to being an informative makers for loss or alteration of the 3p21.3 critical region in cancer (page 20, col 2).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification and the art only provide an association between non-small cell lung cancer (NSCLC) and deletion of RPL14. The specification nor the art provides an association with any cancer, including bladder, head or neck, urothelial, kidneys pancreas, mouth, throat, pharynx, larynx, or esophagus (limitations of Claims 4-10). Shriver teaches that heterozygosity of RPL14 was analyzed in squamous cell carcinoma of the head and neck (SCCHN) and the tumors exhibited normal levels of herterozygosity (page 16, col 2). Therefore, it is unpredictable which cancers are associated with deletion frequency and which cancers are not associated with the aberration. One of skill in the art would be unable to anticipate or predict which of the many cancers are associated with an aberration in hybridization of a RPL14 probe. It would require undue experimentation to analyze the broad range of cancers to determine which additional cancers, if any, are associated with the aberration. Therefore, the specification has not enabled to broad scope of the claims. With respect to Claim 2, since the specification nor the art has provided each of the samples which are directed to specific cancers are associated with cancer, sampling, for example a bladder washing, would be unable to detect lung cancer.

Second, the specification nor the art teaches an association between any aberration in RPL14 and cancer. Aberrations include but are not limited to loss of herterozygosity, aberrations of a trinucleotide repeat, insertions, deletions, translocations, point mutations. The specification analyzes deletion of the region (loss of herterozygosity). The art analyzes the deletion of the region and a trinucleotide

repeat different. Shriver teaches that the aberration of trinucleotide repeat differences was not statistically significant between lung cancer cases and race-matched controls (page 18, col 1). The specification and the art have illustrated a single aberration which is associated with a single cancer type. The art has provided an additional analysis of a second aberration, namely the trinucleotide repeat number, and illustrated that no association was found with the cancer type. Therefore, given the teachings in the art and the specification and the broad scope of the claims, the skilled artisan would not be able to predict without further undue experimentation to determine which aberrations are associated with cancer.

With respect to Claims 57-66, the specification does not specifically teach the detection of deletion of RPL14 as indicative of progression or metastasis of cancer. It is unclear whether the mere deletion of the region is associated with metastasis and progression. Therefore, since neither the specification nor the art provides reasonable guidance to the skilled artisan how to practice the invention as broadly as claimed, the claims lack enablement for the full scope of the claims.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 21, 28, 57-66, 68, 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 21, 28 are indefinite because the claims recite "the probe of Claim 1", however Claim 1 is directed to a method claim. Therefore, it is unclear what probe is being claimed. If the claim is intended to be drawn to a method wherein the method uses a probe, correction is requested. However, if the claim is directed to a product probe claim, the applicant should consider rewriting the claim in independent form.

B) Claims 57-66 are indefinite because the claims do not appear to be a complete method. Claims 57-66 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for predicting the progression or metastasis of non-small cell carcinoma or other carcinoma but the final process step is analyzing DNA from a test sample. Therefore the claims are unclear as to whether the method is a method of predicting the progression or metastasis of non-small cell carcinoma or other carcinoma or analyzing DNA. The claim could be amended to recite, wherein the detection of a deletions at RPL14 is indicative of a progression or metastasis of non-small cell carcinoma.

C) Claim 68 is directed to a method of staging lung of cancer. It is unclear whether the claim was intended to recite "lung cancer" or "cancer of the lung". "Lung of cancer" is confusing. Moreover, the claim is indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for staging lung of cancer but the final process step is determining deletion distribution of a RPL14 gene. Therefore the claims are unclear as to whether the method is a method of staging lung of caner or determining deletion

distribution of a RPL14 gene. As written, one would be unable to stage lung cancer by merely determining the deletion distribution of a gene probe without further guidance or method steps. The claim could be amended to recite, wherein the deletion of RPL14 is indicative of stage *** of lung cancer, provided support may be found in the specification.

D) Claim 87 method steps do not clearly indicate how an individual is identified to be segregated from high risk environment. The claim requires analyzing DNA from a test sample, but the claim does not provide what is being analyzed or what criteria are required to identify an individual is highly susceptible to development of lung cancer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 2, 3, 14-15, 22, 23, 27, 57-58, 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shriver et al. (Mutation Research Genomics, Vol. 406, No. 1, pages 9-23, November 1998).

Shriver et al. (herein referred to as Shriver) teaches chromosome 3p is consistently deleted in lung cancer, oral squamous cell carcinoma and renal cell carcinoma (abstract). Shriver teaches isolating a gene located at 3p21.3, namely the ribosomal protein L14 gene (RPL14)(abstract). Shriver teaches that "genotype analysis of RPL14 shows that this locus is 68% heterozygous in the normal population, compared with 25% in non-small cell lung cancer (NSCLC) cell lines ($p = 0.008$)" (abstract). Shriver teaches using FISH to identify the location of the RPL14 gene (page 12, col 2)(limitations of Claims 15). Shriver teaches that DNA from cells and cell lines derived from six matched normal and tumor samples were analyzed (page 16, col 1). Three tumors showed loss of one RPL14 allele while the remaining three showed alterations in the length of the trinucleotide repeat (Table 3, page 16, col 1). Shriver teaches that heterozygosity of RPL14 was analyzed in squamous cell carcinoma of the head and neck (SCCHN) and the tumors exhibited normal levels of herterozygosity (page 16, col 2). Shriver teaches that the aberration of trinucleotide repeat differences was not statistically significant between lung cancer cases and race-matched controls (page 18, col 1). Shriver teaches that RPL14 is an important event in lung

carcinogenesis in addition to being an informative makers for loss or alteration of the 3p21.3 critical region in cancer (page 20, col 2).

While Shriver does not specifically teach identifying a subject at risk for NSCLC by detecting herterozygosity of RPL14, Shriver clearly illustrates that there is a significant difference between herterozygosity in cancer and control individuals.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the teachings of Shriver that the RPL14 locus is 68% heterozygous in the normal population, compared with 25% in non-small cell lung cancer (NSCLC) cell lines ($p = 0.008$) to indicate that individuals with loss of herterozygosity are more likely to have a predisposition to NSCLC. Shriver specifically teaches that RPL14 is an important event in lung carcinogenesis in addition to being an informative makers for loss or alteration of the 3p21.3 critical region in cancer. The ordinary artisan, prior to determining a test for increased risk or predisposition to a disease, must first determine that the maker/aberration studied is differentially expressed in normal individuals versus diseased individuals. Once an aberration is determined to be significantly over represented or underrepresented in a diseased population, the information may be used to determine additional patients predisposition to the disease. Therefore, using the RPL14 maker for determining a predisposition of a subject to NSCLC would have been obvious in view of the teachings of Shriver.

Conclusion

8. No claims allowable.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Tanaka et al. (Biochemical and biophysical Research Comm. Vol. 243, pages 531-537, February 1998). Tanaka teaches identification of hRL14 and nucleotide sequence.

B) Mao et al. (WO 01/38389, May 2001) teaches a new polypeptide-human ribosomal protein L14.22 which .

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg J. Goldberg
July 8, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600